Remarks/Arguments

This amendment is identical to the amendment filed December 19, 2007, with the exception that the amendment has now been signe. This amendment is submitted in response to the Notice of Non-Compliant Amendment, dated May 27, 2009.

Reconsideration of this application, as amended, is respectfully requested.

I. Status of the Claims and Specification

A. Status of the Claims

After entry of these amendments, claims 1-3, 6-12, 14, 15, 17 and 59 are pending. Claims 4, 16, 18-58 and 60-65 are canceled. Claims 5 and 13 were canceled in the amendment dated March 23, 2007.

Claims 1 and 17 are amended to recite unicellular or filamentous fungi, rather than lower eukaryotic host cell. Support for this amendment is found in the application as filed, at page 11, lines 10-12.

Claim 1 is also amended to recite the step of "introducing into the host cell one or more nucleic acids encoding an α-1,2 mannosidase activity and a GnTI activity." Support for this amendment is found in the application as filed, at paragraph 0123, at original claim 7, and at Example 2.

Claim 1 is also amended to limit the variable "X" (in the formula $GlcNAcMan_XGlcNAc2$) to 3 or 4.

Claims 18-45, 47-58 and 60-65, which were withdrawn from examination as covering a non-elected invention, are now canceled.

Claim 4 is canceled in response to an indefiniteness rejection.

Product-by-process claim 46 is canceled.

Claims 5 and 16 are canceled in view of the amendments to claim 1.

Claim 6 is amended to conform to amended claim 1, and to delete subject matter withdrawn from examination (glycosyltransferase activity).

No new matter is added by these amendments.

B. Status of the Specification

The specification is amended to better describe Figures 4-15, 25, 26, 28, 29 and 32-34, and to refer to the Sequence ID Nos., as requested by the Examiner.

II. Objections to Information Disclosure Statement

The Examiner objects to the Information Disclosure Statement filed November 8, 2005, on the grounds that the reference CM2 (Segawa et al, 1999) was not submitted. In response, a supplemental Information Disclosure Statement, which includes the cited Segawa reference, is submitted with this amendment.

III. **III. Objections to Specification**

The Examiner objects to the specification on the grounds that the specification lacks reference to SEQ ID Nos. assigned to the sequences listed in the figures and throughout the specification (for example, at Figures 4 and 5 and at page 53, paragraph 173. In response, the specification is amended to include the sequence listing references.

In view of the action taken, it is believed that the objections to the specification have been overcome. It is respectfully requested that the objections be withdrawn.

IV. Claim Objections

Claims 6 and 46 are objected to for including non-elected subject matter. The Examiner objects to the recitation of "glycosyltransferase" in claim 6, and the reference to withdrawn claim 44 in claim 46.

Claim 6 is amended to delete "glycosyltranferase."

Claim 46 is canceled.

In view of the action taken, it is believed that the claim objections have been overcome. It is respectfully requested that the objections be withdrawn.

IV. Obviousness-Type Double Patenting Rejections

A. Rejection over claims 1, 3 and 8-12 of U.S. Pat. No. 7,029,872

Claims 1-4, 6, 7, 10, 11 and 14-17 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 3 and 8-12 of U.S. Pat. No. 7,029,872. According to the Examiner, the claims of the '872 patent "are a species of the instant claims."

Applicants respectfully traverse the double patenting rejection, on the grounds that there is a patentable distinction between the claims of this application and the claims of the '872 patent. Independent claims 1 and 3 of the '872 patent require in (a) the selection of a catalytic domain "selected to have optimal

activity in the [endoplasmic reticulum (ER)] or Golgi of said host cell," and in (b) a targeting signal peptide "selected to target the mannosidase enzyme to the ER or Golgi apparatus of the host cell." Claims 1 and 3 also require that the N-glycan structures be produced in the ER or Golgi.

In contrast, independent claim 1 (and dependent claims 2, 3, 6, 7, 10, 11, 14, 15 and 17) require the step of "diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide." As explained in the specification, a lipid-linked oligosaccharide is present at the membrane of the endoplasmic reticulum (*see, e.g.*, parapraph 0016 of the specification), and is not present in the ER or Golgi apparatus of the cell. Since the claimed steps occur at a different location than the steps claimed in the '872 patent, there is no overlap in the claimed subject matter.

Further, the cited claims of the '872 patent recite production of a $Man_5GlcNAc_2$ N-glycan structure. In contrast, the claims of this application as now presented recite production of N-glycan having a $GlcNAcMan_XGlcNAc_2$ core structure, wherein X is 3 or 4.

Accordingly, it is requested that the double patenting rejection over the '872 patent be withdrawn.

B. Rejection over claims 1, 3, 8, 12, 13, 16-18 and 28 of copending Appl. Ser. No. 10/371,877

Claims 1-4, 8-11, 14-17 and 59 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 3 , 8, 12 13, 16-18 and 28 of copending patent application U.S. serial no. 10/371,877. A copy of the pending claims of application serial no. 10/371,877, as set forth in the October 26, 2007 amendment, is attached at Exhibit A.

The Examiner states that both sets of claims are drawn to making N-glycan recombinant glycoprotein in a eukaryotic host cell. The Examiner states that the '877 application claims are narrower than the pending claims, because the '877 claims recite "the alpha-1,2 mannosidase catalytic domain." The Examiner also notes the recitation of "NeuNAc-Gal-GlcNAc-Man ('877, claim 13; '240 claim 15), and the use of P. pastoris ('877 claim 16; '240 claim 17).

Applicants respectfully traverse the double patenting rejection, on the grounds that there is a patentable distinction between the claims of this application and the '877 application claims. Independent claim 1 of the '877 application requires production of N-glycans "upon passage of the recombinant glycoprotein through the ER or Golgi apparatus of the host cell."

In contrast, as noted above with respect to the double patenting rejection over the '872 patent, the pending claims require the step of "diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide." As explained in the specification, a lipid-linked oligosaccharide is present at the membrane of the endoplasmic reticulum (*see, e.g.*, parapraph 0016 of the specification), and is not present in the ER or Golgi apparatus of the cell. Since

the claimed steps occur at a different location than the steps claimed in the '877 application, there is no overlap in the claimed subject matter.

Further, the cited claims of the '877 application require production of a $Man_5GlcNAc_2$ N-glycan structure. In contrast, the claims of this application as now presented recite production of N-gylcan having an $GlcNAcMan_XGlcNAc_2$ core structure, wherein X is 3 or 4.

Accordingly, it is requested that the double patenting rejection over the '877 application be withdrawn.

C. Rejection over claims 1-15 and 18-20 of copending Appl. Ser. No. 11/187,066

Glycoprotein claim 46 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-15 and 18-20 of copending patent application serial no. 11/187,066.

Claim 46 is canceled, thereby obviating the double patenting rejection over the '066 application. Hence, it is requested that the double patenting rejection over the '066 application be withdrawn.

V. Rejections Under 35 U.S.C § 112, First Paragraph

At pages 9-15, claims 1-4, 6-12, 14-17, 46 and 59 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification is not enabling for methods comprising introducing "a transgene construct comprising 988-1296 nucleotides of yeast SEC12 operably linked to an N-terminal deletion of mouse alpha-1,2-mannosidase 1A gene and (2) a transgene construct comprising the first 120 bp of S. cerevisiae MNN9 gene operably linked to human GnTI, which was missing the first 154 bp.

The Examiner also asserts that the claims lack enablement for a method which comprises "disrupting Och1 and alg3 in P. pastoris and comprises introducing transgene constructs 1) a construct comprising 988-1296 nucleotides of yeast SEC12 operably linked to an N-terminal deletion of mouse alpha-1,2-mannosidase 1A gene and 2) a transgene construct comprising the first 120 bp of S. cerevisiae MNN9 gene operably linked to human GnTI, which as missing the first 154 bp.

At page 10, the Examiner objects to the recitation of "any host cell and expressing any glycosidase activity." Claim 1 is now amended to recite the host cell of a "unicellular or filamentous fungus," and the glycosidase activities of " an α-1,2 mannosidase activity and a GnTI activity." ; The claims are now asimH

VI. Rejections Under 35 U.S.C § 112, Second Paragraph

Claim 4 stands rejected under 35 U.S.C § 112, second paragraph, as indefinite. The Examiner states that the recitation of producing an N-glycan does not introduce any new limitations into independent claim 1. In response, claim 4 is canceled, thereby obviating the indefiniteness rejection.

VII. Rejections Under 35 U.S.C. § 102

A. Rejection of Method Claims

The claimed method of the invention is fundamentally different from the processes described in both the Gerngross '872 patent and in Chiba. The claims cover a method for producing a recombinant glycoprotein in a unicellular or filamentous fungus host cell. The claims require the step of "diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure." The claims further require "introducing into the host cell one or more nucleic acids encoding an α-1,2 mannosidase activity and a GnTI activity, " thereby producing in the host cell "recombinant glycoproteins having N-glycans attached thereto comprising $GlcNAcMan_XGlcNAc_2$ core structures, wherein X is 3 or 4."

As explained below, neither of the cited references, Gerngross '872 or Chiba, describe the claim limitation of "diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure." Instead, both Gerngross '872 and Chiba add a sugar residue to the 1,6 arm of a protein-bound oligosaccharide.

1. Rejection over U.S. Pat. No. 7, 029,872, to Gerngross

Claims 1-4, 6, 7, 10, 11, 14-17 and 46 stand rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Pat. No. 7, 029,872, to Gerngross.

The Examiner states at page 16 of the office action that Gerngross '872 "has a common inventor with the instant application." However, this is incorrect. Tillman Gerngross is the sole inventor of the '872 patent, and is not an inventor of the claimed invention.

The Examiner states that Gerngross "describes a method of making recombinant glycoprotein comprising an N-glycan structure in a eukaryotic host cell, wherein the method comprises diminishing or depleting one or more enzymes that transfer a sugar residue to the 1,6 arm of a lipid –linked oligosaccharide structure." However, Gernrgross '872 teaches transfer of a sugar residue to the 1,6 arm of a protein–linked oligosaccharide structure. Gerngross does not teach or contemplate transfer of a sugar residue to the 1,6 arm of a lipid–linked oligosaccharide structure, as required by the claims.

Gerngross describes glycosylation of ogligosaccharides by mannosyltransferases residing in the Golgi. See col 10, l. 35-38. Gerngross states that "mutants of S. cerevisiae, deficient in mannosyl transferase activity (e.g. och1 or mnn9 mutants) have shown to be non-lethal and display a reduced mannose content in the oligosaccharide of yeast glycoproteins." Col. 10, l. 41-44.

Gerngross is predominantly directed to producing glycoproteins having a $Man_5GlcNAc_2$ core structure (see, e.g., col. 11-12). The only references to a $GlcNAc_3Man_2$ structure are in Example 3, which describes engineering of a strain with a mannosidase II, and in Table 6, at column 24. The third to sixth entries in Table 6 describe oligosaccharide structures having $Man_{3-4}GlcNAc_2$ cores structures. Each describes gene deletions at OCH1, MNN4 and MNN6. Gerngross describes formation of a $GlcNAcMan_3GlcNAc_2$ structure at Figure 1.B after action of the enzyme mannosidase II, in the Golgi, when the oligosaccharide is bound to the protein. Table 6, at column 24, also describes a method of forming a $GlcNAc_{2-4}Man_3GlcNAc_2$ core structures. Here, again, the formation of this oligosaccharide requires action of the enzyme mannosidase II, when the oligosaccharide is bound to the protein.

Hence, Gerngross does not teach the claimed method.

2. Rejection over Chiba et al, *J Biol. Chem* 1998, 273:26298-26304

The Examiner states that Chiba et al. "teach that CPY was used as a reporter glycoprotein to assess the glycosylation pattern of a triple mutant strain of yeast, wherein the yeast was a mutant for Och1, Mnn1, and Mnn4." The Examiner contends that "Chiba et al. meet all the steps" of claim 1.

Applicants traverse, on the grounds that Chiba does not meet a key limitation of claim 1, the step of "diminishing or depleting the activity of one or more enzymes in the host cell that transfers a sugar residue to the 1,6 arm of a lipid-linked oligosaccharide structure."

Chiba depicts formation of a $GlcNAc_2Man_3GlcNAc_2$ structure only at Figure 1, left hand column. Chiba teaches the formation after the action of the enzyme mannosidase II, in the Golgi, when the oligosaccharide is bound to the protein.

Hence, Chiba does not teach the claimed method.

B. Rejections of Product-by-Process Claim 46

Product-by-process claim 46 stands rejected over each of Kornfeld, *J Biol. Chem* 1983, 258:7907-7910, Wagner et al, *Glycobiology* 1996 6:165-175, and Velasco et al, *J. Cell Biol* 1993 122:39-51.

Claim 46 is canceled, thereby obviating these rejections.

In view of the action taken and arguments made, it is believed that the anticipation rejections have been overcome. It is respectfully requested that the rejections be withdrawn.

VII. Conclusion

In view of the action taken and arguments made, all pending claims 1-3, 6-12, 14, 15, 17 and 59 are are enabled by the specification, and are not anticipated by the cited prior art. All pending claims 1-3, 6-12, 14, 15, 17 and 59 are now in condition for allowance.

Favorable action is earnestly solicited.

Respectfully submitted,

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